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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,587	05/03/2002	Dan L. Eaton	P3230R1C001-168	4546

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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,587	EATON ET AL.	
	Examiner	Art Unit	
	Claire M Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/24/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

The rejection of claims under 35 USC 112, second paragraph, is withdrawn in view Applicants' arguments.

The rejections of claim 6 are moot in view of the cancellation of the claim.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Inventorship

In view of the papers filed 9/24/04, the inventorship in this nonprovisional application has been changed by the deletion of Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, and Colin K. Watanabe.

Response to Amendment

The Declarations of Drs. Grimaldi, Polakis and Ashkenazi under 37 CFR 1.132 filed 9/24/04 are insufficient to overcome the rejection of claims 1-8, 11-14 and 16-20 based upon 35 USC 101/112, first paragraph, enablement, as set forth in the last Office action because: they are not sufficient to overcome the rejections for the reasons discussed in response under the rejections below. While statements are made in the Polakis and Grimaldi Declarations concerning correspondence of DNA amplification and encoded polypeptide increase in particular cell types, there remain issues about the correspondence tied to insufficiency of disclosure. While the Declaration of Ashkenazi discusses the importance of overexpression of genes in cancers, the instant case shows an underexpression in the tumors. The Grimaldi Declarations are not sufficient to support a specific and substantial or well-established utility for the claimed invention. The utility and enablement for the claims are further discussed under the appropriate section for the rejections below.

Claim Rejections - 35 USC § 101/ 112, First Paragraph

Claims 1-5 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office action on pages 2-3.

Applicants argue that the USPTO must establish that it is more likely than not that one of skill the art would doubt the truth of the statement of utility, namely that the gene and encoded PRO1357 protein is differentially expressed in certain cancers compared to normal tissue and useful as a diagnostic tool. The argument has been fully considered, but is not persuasive. Utility requires that the skilled artisan be able to use the claimed invention. The specification does not provide a specific and substantial or a well-established use. Applicants have provided a single analysis without any relative range for basing a utility of underexpression. It is not disclosed what type(s) of lung or stomach tumor was analyzed. It is not clear if the finding can be generalized to all tumors from that tissue type. The skilled artisan would not know if the results were significant or under what conditions a difference in expression could be detected. It is not clear, for example, if underexpression was detected in 1/10 or 10/10 stomach adenocarcinoma tumors. As stated in the previous Office action:

There is no guidance on how to use this information. No levels (relative or absolute) are disclosed. This information is too sparse to allow the encoding polynucleotide to be used as a diagnostic marker for stomach or lung tumor. Because it is not known if the nucleic acid is involved in causing (or suppressing) the tumor, the skilled artisan could not use it therapeutically as target for treatment of a tumor.

The disclosure lacks information and guidance to support a specific and substantial use for the claimed invention. Even if tissue samples are pooled, about which the first Grimaldi Declaration says, "That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type," [paragraph 5] without knowing the range of variation there is insufficient guidance. If a clinician took a stomach tissue sample from a patient with suspected stomach cancer, what is the likelihood that when compared with normal tissue, the level of nucleic acid of SEQ ID NO:77 from the patient would be lower? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a

pooled sample or could it be from a single individual? While the 6th paragraph of the first Grimaldi Declaration says that the detection technique used in the specification makes it "reasonable to assume that any detectable differences seen between two samples will represent at least a two-fold difference in cDNA," that statement still does not answer the questions raised above and does not place a specific and substantial use of the nucleic acid or encoded polypeptide in the skilled artisan's hand. The statement that the relative difference in expression is what is important is generally true, but without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of stomach or lung tissue that can used, and other questions, the specification has not provided the invention in a form usable by the skilled such that significant further experimentation was unnecessary.

Applicants argue that if the gene is differentially expressed in cancer versus non-cancer tissue, then its mRNA and encoded polypeptide and antibody which binds the polypeptide are useful as diagnostics. The argument has been fully considered, but is not persuasive. There is no evidence that the polypeptide of PRO 1357 is underexpressed in stomach or lung tumors. Further, if one cannot use the encoding nucleic acid as a diagnostic tool for tumors, then one cannot use the encoded polypeptide or cognate antibody either. The Declarations of Grimaldi (second declaration) and Polakis discuss the likelihood that if the nucleic acid is differentially expressed in tumors then the encoded polypeptide will also be. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding decreased mRNA levels of PRO1357 in tumor samples relative to normal samples.

Only relative gene expression data was presented. Second, the declaration does not provide data such that the Examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a micoarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). From the second Grimaldi Declaration, a paragraph is cited by Applicants (p. 11 of response) that says even in the rare case where protein expression does not correlate with mRNA expression, this is still important information for providing more accurate tumor classification information in the determination of suitable therapy. However, in the instant application it is not disclosed whether or not the polypeptide levels correlate with nucleic acid (either DNA or mRNA) levels. So one cannot base the use of the nucleic acid on the expression of the polypeptide or vice versa. The statements of Grimaldi (see paragraph bridging pp. 7-8 of response) are echoed in the Ashkenazi declaration.

Applicants argue (p. 11) the declaration filed by Dr. Ashkenazi under 35 USC 1.132 supports the gene amplification data in the present application because even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, that in itself provides important information for cancer diagnosis and treatment. There is no evidence that clinicians use information about a gene product *not* being overexpressed as a basis for deciding to not treat a patient with an agent that targets that gene product. This is a hypothetical utility not disclosed in the specification.

Applicant refers to three additional articles (Orntoft et al., Hyman et al. and Pollack et al.) as providing evidence that gene amplification generally results in elevated levels of the encoded

polypeptide. Applicant characterizes Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Applicant characterizes Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicant characterizes Pollack et al. as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. The arguments relating to these references has been fully considered but is not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region (see for example, p 44, last paragraph of col. 1). Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO1357 in the instant specification. That is, it is not clear whether or not PRO1357 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft et al. is not clear. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Pollack et al. also noted contradictory results found by another research group, noting that, "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors; resolution of this issue will require further studies" (p. 12968, end of first paragraph). This leads again to the issue of unpredictability. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the later three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of potential cancer therapeutics, but also clearly

imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO1357 polypeptides and antibodies have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Indeed, there is evidence in the art to refute generalizations about gene/protein correlations. For example, Haynes et al. (Electrophoresis 19 : 1862-1 87 1 , 1998) studied 80 proteins relatively homogenous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1 863, second paragraph, and Figure 1). Konopka et al. (PNAS, 83:4049-52. 1986) states that, "Protein expression is not related to amplification of the *abl* genenbut to variation in the level of bcr-abl mRNA production from a single Ph1 template" (see abstract). Konopka et al. also provide evidence showing lack of correlation between gene amplification and increased polypeptide levels. Haynes et al. provides evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon (p. 1863). Haynes et al. used yeast as an art-accepted model for eukaryotic systems. Given how small the unknown amount that DNA copy number of PRO1357 decreased in tumors, and the evidence provided by Haynes et al., Hu et al. (discussed above) and Konopka et al., one skilled in the art would not have assumed that a small decrease in gene copy number would be accompanied by a significantly altered mRNA or polypeptide levels. The level of decrease of the encoding nucleic acid is not disclosed. One skilled in the art would have to do further research to determine whether or not the PRO1357 polypeptide levels decreased significantly in the tumor samples. Such further research requirements makes it clear that the asserted utility is not yet in currently available form, *i.e.,* it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention

> with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Note that the invention must have a specific and substantial utility.

Applicants argue that a specific utility for PRO1357 has been provided because the encoding gene is associated with a specific disease. The argument has been fully considered, but is not persuasive. If the specification supported the direct association of the PRO1357 nucleic acid of SEQ ID NO:77 with particular or all stomach and lung tumors, then at least for the nucleic acid the requirements of utility might be satisfied. However, for the reasons set forth in the previous Office action and as discussed above, this has not been done. Further, even assuming the nucleic acid had a diagnostic utility, the encoded protein and its cognate antibody would not (see above).

Applicants argue that the teachings of Hanna et al. show that for Her-2, to diagnose breast cancer both gene product presence as well as amplification of the gene itself provides the most complete information. The argument has been fully considered, but is not persuasive. Hanna et al. say these testes are used more or less independently, with the protein test used first, followed by the gene test if the protein test is negative (col. 2, third full paragraph). The protein test is only necessary to determine the appropriateness of antibody therapy. Also, it is stated in the same paragraph that "In general, FISH [gene] and IHC[protein] results correlate well. However, subsets of tumors are found which show discordant results; i.e., protein overexpression without gene amplification or lack of protein overexpression with gene amplification. The clinical significance of such results is unclear." Therefore, the issues of Her-2 cannot be generalized to any gene expressed in a tumor.

Claims 1-5 remain also rejected under 35 U.S.C. 1 12, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above and in the previous Office action, one skilled in the art clearly would not know how to use the claimed invention.

The arguments for this rejection were presented with those of the rejection under 35 USC 101 and also answered above.

Claim Rejections - 35 USC § 102

Claims 1-5 remain rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/16318 or WO 00/12708 for the reasons set forth in the previous Office action.

Applicants argue that the instant application receives an effective filing date of 9/10/98 because SEQ ID NO:77 and 78 were disclosed therein. The argument has been fully considered, but is not persuasive. Because the claims do not meet the requirements of 35 U.S.C. § 112, first paragraph, as discussed above, and the earlier application likewise do not meet those requirements, the instant application does not receive benefit of priority to earlier filed applications. Even though SEQ ID NO:77 and 78 were previously disclosed, use thereof has not been established as discussed above.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 8:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (703) 872-9306. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.
Patent Examiner, Art Unit 1646
December 6, 2004

ELIZABETH KEBKABER
PRIMARY EXAMINER